Supplemental table 1. Bone tropism

Cancer type	Mechanisms involved	References
ER+ oriented Breast cancer	E-cadherin on cancer cells interacts with N-cadherin of osteogenic cells to activate the mTOR pathway and promote early-stage bone colonization of ERα+ breast cancer cells	(Wang et al., 2015)
	Calcium influx from osteogenic niche cells to cancer cells through gap junction promotes bone metastasis	(Wang et al., 2018)
	MSK1 prevents the progression of bone metastasis in ERα+ breast cancers, and loss of MSK1 promotes cancer cells homing and colonization in bone	(Gawrzak et al., 2018)
	LIFR-STAT3-SOCS3 signaling sustains the dormancy of breast cancer cells in bone, which is repressed by hypoxia	(Johnson et al., 2016)
	Dormant breast cancer cells reside in E-Selectin and CXCL12 rich perisinusoidal niches, and the interaction between cancer cells and niches enables the homing and dormancy of cancer cells in the bone	(Price et al., 2016)
TNBC oriented Breast cancer	Src activation enhances the survival response to bone environmental factors, CXCL12 and TRAIL, by regulating AKT pathway in breast cancer cells, and thereby promotes the metastatic outgrowth in bone	(Zhang et al., 2009)
	Cancer-associated fibroblasts mimic bone environment by secreting CXCL12 and IGF1, and select bone metastatic seeds with high Src activity in triple negative breast cancer	(Zhang et al., 2013)
	Hypoxic secretome derived from ER- tumors increases the activity of osteoclasts through secretion of LOX, and therefore creates a tumor-promoting, osteolytic niche before the arrival of cancer cells	(Cox et al., 2015)
	Dormant breast cancer cells reside in perivascular niches, and endothelial cells derived TSP1 sustains the quiescence of cancer cells	(Ghajar et al., 2013)
	Perivascular niches protect cancer cells from chemotherapy through integrin-mediated interactions between cancer cells and endothelial cells	(Carlson et al., 2019)
	Silencing of IRF7 and related pathways enables the escape of immunosurveillance to promote bone metastasis	(Bidwell et al., 2012)
	Secretome analysis of bone tropic breast cancer cells reveals unique secreting proteins associated with bone metastasis, including salivary cystatins, plasminogen activators, and collagen functionality proteins.	(Blanco et al., 2012)
	Tumor cell-derived Jagged1 activates NOTCH pathway of bone cells, stimulates IL-6 secretion from osteoblasts and promotes the osteoclastogenesis. Jagged1 blocking by γ-secretase inhibitors reduces bone metastasis.	(Sethi et al., 2011)
	Chemotherapy induces the expression of Jagged1 on osteoblasts to support cancer cells survival. Therapeutic antibody targeting Jagged1 sensitizes bone metastasis to chemotherapy.	(Zheng et al., 2017)
	Tumor expression of integrin $\alpha_v\beta_3$ contributes to the early phases of bone metastasis by promoting cancer cell invasion and bone resorption.	(Pecheur et al., 2002; Zhao et al., 2007)
	RON tyrosine kinase on the osteoclasts mediates macrophage-stimulating protein (MSP) signaling induced osteolysis in breast cancer bone metastasis	(Andrade et al., 2017)
HER2+ oriented Breast cancer	Osteomimetic properties of bone tropic cancer cells facilitate the colonization in bone environment by expressing bone matrix proteins and growth factors.	(Logothetis and Lin, 2005)
Prostate cancer	Disseminated prostate cancer cells directly compete with HSC for niche support, and utilize similar mechanisms, such as CXCR4/CXCL12 and Runx2, to colonize bones	(Shiozawa et al., 2011)
	Prostate cancer cells home to bone utilizing the CXCR4/CXCL12 pathway	(Taichman et al., 2002)
	Activation of Ras-related protein 1 enhances prostate cancer cells migration and invasion through the integrin pathway	(Bailey et al., 2009)
	Bone metastatic prostate cancer cells respond to bone cells derived PDGF through expression of PDGFRα, which enhances Akt/PKB signaling	(Dolloff et al., 2005)
	Androgen stimulates the expression of CX3CL1 in the bone environment, which interacts with CX3CR1 on prostate cancer cells to facilitate bone metastasis	(Jamieson et al., 2008)
Lung cancer	Silencing of DDR1 impairs the early colonization of lung cancer cells in the bone	(Valencia et al., 2012)
	CD24 expression is required for lung cancer bone metastasis	(Okabe et al., 2018)
	TCF4, PRKD3, MCAM, SUSD5 are part of a gene signature for lung cancer bone metastasis	(Vicent et al., 2008)
	Increased BSP (bone sialoprotein) expression in primary NSCLC predicts bone metastasis	(Papotti et al., 2006)
Myeloma	MMP-2 inhibition can reduce multiple myeloma progression in bone	(Shay et al., 2017)
	Osteoclasts contribute to sensory neuron (SN) activation in multiple myeloma by promoting an acidic ME and activation of acid-sensing channel 3 (ASIC3). Targeting ASIC3 decreases bone pain	(Hiasa et al., 2017)
Melanoma	Horizontally transferred tumors from highly metastatic melanoma cells through exosomes mobilizes BM progenitor cells and prepares the pre-metastasis niches for cancer cells	(Peinado et al., 2012)
	Targeting mutant BRAF (V600E) with PLX4032 results in CPR or partial tumor regression in most patients	(Flaherty et al., 2010)
	Increased expression of Smad7 in human melanoma cells impairs bone metastasis	(Javelaud et al., 2007)
Bladder cancer	High FGFR2 may promote metastasis by regulating mesenchymal to epithelial transition	(Chaffer et al., 2006)
	PI3K/AKT and GSK3B/b-catenin regulate ZEB1 to promote bone colonization in bladder cancer	(Wu et al., 2012)

Supplemental table 2. Liver tropism

Cancer type	Mechanisms involved	References
TNBC oriented Breast cancer	Claudin-2 promotes breast cancer liver metastasis by facilitating tumor cell interactions with hepatocytes	(Tabaries et al., 2012)
	Afadin cooperates with claudin-2 to promote breast cancer metastasis	(Tabariès et al., 2019)
	Kupffer cells in the liver uptake exosomes expressing integrin αvβ5 and release pro-inflammatory S100A8 which leads to liver tropism.	(Hoshino et al., 2015)
Lung cancer	Collagen IV-conveyed signals can regulate CCL5 and CCL7 production and promote liver metastasis	(Vaniotis et al., 2018)
Melanoma	Notch controls hepatic metastasis via modulation of hepatic endothelial cell adhesion molecules ICAM1	(Wohlfeil et al., 2019)
Colorectal cancer	Sinusoidal endothelial cells produce LSECtin to promote metastasis by inhibiting the hepatic T cell immune response	(Tang et al., 2009)
	LSECtin promotes the migration of colorectal cancer cells and increases the expression of c-Met in these cells to induce liver metastasis.	(Zuo et al., 2013)
	Cadherin-17 interacts with integrin α2β1 to regulate cell proliferation and adhesion in colorectal cancer cells causing liver metastasis	(Bartolomé et al., 2014)
	Targeting ALDOB or its upstream regulator GATA6 reduces liver metastasis growth	(Bu et al., 2018)
	miR885-5p plays a critical role in liver metastasis by regulating EMT signaling through the expression of CPEB2/TWIST1	(Siu-Chi Lam et al., 2017)
	Citrullination of the ECM by cancer cell-derived PAD4 promotes liver metastases growth	(Yuzhalin et al., 2018)
	The NLRP3 inflammasome is activated in macrophages by macrophage–cancer cell crosstalk and results in faster migration of colorectal cancer cells	(Deng et al., 2019)
	Cancer cells attach to endothelial fibronectin deposits via talin1, a major component of focal adhesions.	(Barbazán et al., 2017)
Gastric cancer	Exosome-delivered EGFR regulates liver ME to promote gastric cancer liver metastasis though miR26/HGF/c-MET pathway	(Zhang et al., 2017)
	SYT7 knockout inhibits the proliferation of GC cells, indicated by increased apoptosis with activated caspase and loss of mitochondria membrane potential, G2/M cell-cycle arrest and attenuated cell migration, invasion, and adhesion.	(Kanda et al., 2018)
Pancreatic cancer	The MIF enriched exosomes released by pancreatic cancer cells activates Kupffer cells to secrete TGFβ and triggers stellate cells to produce fibronectin to recruit bone marrow-derived macrophages and induce liver-specific metastasis	(Costa-Silva et al., 2015)
	MAMs can secrete granulin to activate hepatic stellate cells and induce a fibrotic ME that sustains metastatic tumor growth	(Nielsen et al., 2016)

Supplemental table 3. Lung tropism

Cancer type	Mechanisms involved	References
Breast Cancer	Tumor cells express GALNT14 to overcome the inhibitory effect of lung-derived BMPs on cancer stem cell self-renewal	(Song et al., 2016)
	Chemokine receptors CXCR4 and CCR7 are highly expressed in human breast cancer cells which are attached to the lung by CXCL12 and CCL21.	(Müller et al., 2001)
	Chemotherapy-induced EVs promote metastasis by increasing CCL2 and recruit pro-metastatic monocytes.	(Keklikoglou et al., 2019)
	Localized activation of endothelial FAK and E-selectin in the lung vasculature mediates the initial homing of metastatic cancer cells to specific foci in the lungs	(Hiratsuka et al., 2011)
	Lysyl oxidase-like protein LOXL2 promotes lung metastasis of breast cancer through regulating Snail1 and expression of several cytokines that promote premetastatic niche formation	(Salvador et al., 2017)
	The Rho exchange factors Vav2 and Vav3 play important roles in breast cancer and control a lung metastasis-specific transcriptional program	(Citterio et al., 2012)
	Metastatic cancer cells produce Tenascin C to induce Notch and WNT pathways and initiate metastasis	(Oskarsson et al., 2011)
	ID1 facilitates sustained proliferation of lung metastatic cells during the early stages of metastatic colonization, subsequent to extravasation into the lung parenchyma.	(Gupta et al., 2007)
	TGFβ primes breast tumors for lung metastasis seeding through ANGPL4 mediated extravasation	(Padua et al., 2008)
Melanoma	Tumor exosomal RNAs activate TLR3 signaling in alveolar type II cells to induce chemokine secretion and recruit neutrophils to build up the pre-metastatic niche	(Liu et al., 2016)
	Melanoma EVs downregulate IFNRA1 and CH25H in normal cells to facilitate lung metastasis.	(Ortiz et al., 2019)
	Lung fibroblasts promote metastatic colonization through upregulation of stearoyl-CoA desaturase 1 in tumor cells	(Liu et al., 2018)
	CX3CR1 positive patrolling monocytes are recruited by endothelial cells to control tumor metastasis to the lung	(Hanna et al., 2015)
	HPCs are recruited by fibroblasts through VEGFR1/integrin α4β1/fibronectin to promote vascular permeability.	(Kaplan et al., 2005)
	Lung inflammation promotes metastasis through neutrophil protease-mediated degradation of TSP-1	(El Rayes et al., 2015)
	Tumor-derived SPARC drives vascular permeability and extravasation through endothelial VCAM1 signaling to promote metastasis	(Tichet et al., 2015)
Colorectal cancer	MMP9 induction by vascular endothelial growth factor receptor-1 is involved in lung-specific metastasis	(Hiratsuka et al., 2002)
Prostate cancer	Bone marrow-derived Gr1+ cells generate a metastasis-resistant ME via induced secretion of TSP-1 by tumor-secreted prosaposin	(Catena et al., 2013)

Supplemental table 4. Brain tropism

Cancer type	Mechanisms involved	References
Breast cancer	PTEN loss induced by tumor exosomal miRNA primes brain metastasis outgrowth	(Zhang et al., 2015)
	miR509 suppresses brain metastasis of breast cancer cells by modulating RhoC and TNFα	(Xing et al., 2015)
	Activation of the c-Met pathway mobilizes an inflammatory network in the brain to promote brain metastasis of breast cancer	(Xing et al., 2016)
	Loss of XIST in breast cancer activates MSN-c-Met and reprograms microglia via exosomal miRNA to promote brain metastasis	(Xing et al., 2018)
	Cathepsin S specifically mediates blood-brain barrier transmigration through proteolytic processing of the junctional adhesion molecule, JAM-B.	(Sevenich et al., 2014)
	Invadopodia are chemosensing protrusions that guide cancer cell extravasation to promote brain tropism in metastasis	(Williams et al., 2019)
	Brain metastatic cancer cells release miRNA-181c-containing EVs capable of destructing blood-brain barrier.	(Tominaga et al., 2015)
	Serpins promote cancer cell survival and vascular co-option in brain metastasis	(Valiente et al., 2014)
	miR1258 suppresses breast cancer brain metastasis by targeting heparanase, a potent pro-tumorigenic, pro-angiogenic and pro-metastatic enzyme.	(Zhang et al., 2011)
	Carcinoma–astrocyte gap junctions promote brain metastasis by cGAMP transfer	(Chen et al., 2016)
Melanoma	Astrocytes with active STAT3 signaling can facilitate metastasis by inhibiting both the innate and acquired immune system.	(Priego et al., 2018)
Lung cancer	Elevated PLGF contributes to small-cell lung cancer brain metastasis	(Li et al., 2013)
	The interaction between lung cancer cells and astrocytes via specific inflammatory cytokines, including MIF, IL-8 PAI-1, IL-6, TNFα, and IL-1β, promotes tumor cell proliferation	(Seike et al., 2011)